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BY FACSIMILE

CASE BP8935B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BOULOS ET AL.
APPLICATION NO: 10/047,583
FILED: January 14, 2002
FOR: VITAMIN FORMULATION FOR CARDIOVASCULAR HEALTH

Art Unit: 1616
Examiner: Frank Choi

Commissioner for Patents
Box 1450
Washington, D.C. 202313-1450

DECLARATION OF ATEF BOULOS

I, Atef Boulos, declare and say as follows:

1. I am a United States citizen residing at 42 Dominic Drive, Rockaway, NJ 07866.

2. I am presently employed by Bristol-Myers Squibb Company, assignee of the above-identified application ("the Application") in the capacity of Senior Research Investigator and have been employed by Bristol-Myers Squibb since September 23, 1996. Prior to such time I was employed by Smith Kline Beecham (Parsippany, N.J.) as a Senior Research Scientist.

3. I am a graduate of the New Jersey Institute of Technology, (N.J., U.S.A.), having received an M.S. in Chemistry in 1984, as well as a graduate of the College of Pharmacy (Cairo, Egypt) having received an M.S. in Pharmacy in 1972.

4. In my various positions as listed in paragraph 2 above, I acquired extensive experience in the manufacture of tablets and caplets and in the formulation of compositions compressible into tablets and/or caplets. My educational background and work experience qualify me as one skilled in the art to which the Application relates.

5. I am a co-inventor of the Application and am thoroughly familiar with its contents, the office Action of October 17, 2003 and the prior art references cited therein. The combination of references cited as a basis for holding Applicants' claimed invention obvious would not enable one skilled in the art to solve the problem of incorporating a high dose of encapsulated Vitamin E, which when compressed into a tablet or caplet retains the oily liquid Vitamin E within the tablet or caplet matrix during long term storage, thereby providing a stable tablet.

6. The Examiner has cited US Pat. #6,0340,645 ("Tritsch et al.) in view of US Pat #5,925,381 ("Boyle et al."), EP 0595005 and US Pat. # 4,486,435 ("Schmidt et al.") against Applicants' claims. Each of these patents/applications describe compositions and processes for making a raw material possibly comprising Vitamin E that facilitates the handling (including tabletting) of such compositions.

7. None of the references teach, alone or in combination, that a stable tablet may be formed that incorporates at least 100 IU of Vitamin E and further contains minerals and vitamins. Rather, each reference describes raw Vitamin E formulations that are suited for the manufacture of tablets according to procedures known in the art. Only Tritsch gives actual examples of tablets containing the raw Vitamin E formulation, only one of which (Example #6 – corresponding to 210 IU per unit dose or 280 mg in a 75% formulation), contains over 100 IU per unit dose. (The other two Tritsch examples containing Vitamin E in a tablet contain well under 100 IU/unit dose (See Example 7 and 8, each corresponding to 53 IU per unit dose or 70.7 mg in a 75% formulation)).

8. The Tritsch tablet of Example #6 that contains 210 IU per unit dose in the tablet dos NOT contain vitamins and minerals as required in Applicants' amended claims. In fact, Tritsch does not suggest the desirability of a formulation further containing vitamins and minerals, nor a method of finding Applicants' particular claimed compositions, that will provide a stable multivitamin/mineral tablet containing more than 100 IU of Vitamin E.

9. To demonstrate the criticality of the use of precipitated silica and calcium silicate in the relative amounts specified by Applicants' claims and in a total amount of at least 4%, tests were carried

out by me or within my project group. These tests and results obtained are accurately set forth in Exhibits 1 and 2 attached hereto and made a part hereof.

Each of the compositions listed in Exhibits I and II were evaluated for tablet stability by looking for increased hardness with increased compression force plus an increase in disintegration time only with an increase in hardness.

An increase in tablet disintegration time without a corresponding increase in tablet hardness is indicative of the encapsulated Vitamin E leaching out into the tablet matrix (an unstable tablet).

An increase in tablet disintegration time without a corresponding increase in tablet hardness as compression force is increased is indicative of the encapsulated Vitamin E leaching out and coating the outside of the tablet and thereby impeding tablet disintegration (an unstable tablet).

10. As presented in the table "Summary of Development Batches", experiments 122, 124, 128, 129, 133, 134 and 135 incorporate 3.0- 3.8% (weight/weight) of silicas in addition to the silicas contained in the encapsulated Vitamin E manufactured by BASF and/or Roche.

    Similarly, experiments 135, 127, 138, 142, 143 and 205 incorporated 4.54% to 7.50% (weight/weight) added silicas as specified for each experiment under the column "Total Added Silica."

    The criterion for the tablet performance was established based on applying the minimum compression force to achieve the desired hardness (30 scu) while not increasing the disintegration time for the compressed tablet.

11. The test results of Exhibits 1 and 2 show that when 3 to 4% total silica was used, increasing the compression force did not produce a corresponding increase in tablet hardness. This was due to the encapsulated Vitamin E leaching out into the tablet matrix which in turn reduced the compressibility of the pharmaceutical aids by reducing their bonding character.

12. The test results of Exhibits 1 and 2 also show that a composition having a high concentration of Vitamin E, 7.5% w/w total silicas and having a precipitated silica to calcium silicate ratio (3.5% precipitated silica (Syloid 244 FP®) and 4.0% calcium silicate) in accordance with Applicants' claims, could be compressed into tablets having 30 scu hardness at 16.5 kN of compression force without extending the tablets' disintegration time.

The test results of Exhibits 1 and 2 show that a stable and acceptable tablet that contains a high dose of Vitamin E cannot be produced on a commercial scale unless the tablet contains precipitated silica and calcium silicate in the ratio spelled out in Applicants' claims and in a total amount of at least 4%, as is also called for by Applicants' claims.

One skilled in the art of tabletting would not be able to produce a tablet that contains a high concentration of Vitamin E oil, and that possesses the requisite hardness and disintegration time and does not evidence physical instability such as capping, unless he/she employed precipitated silica and calcium silicate as tablet components in the ratio and in the total amount called by Applicants' claims.

I hereby state that all statements made of my own knowledge are true and that all statements made by me on information and belief are believed to be true. Furthermore, I make this declaration with the knowledge that willful false statements and the like are punishable by fine and imprisonment, or both (18 USC 1001) and may jeopardize the validity of the Application or any patent issuing thereon.

Atef Boulos

12/16/03
Date

Exhibit 1
Summary of Development Batches

BATCH #	DESCRIPTION		Total added silica	Tablet Weight	Comp. Force vs. Hardness		
122	Cab-O-Sil	0.75%	3.01%	1196.9 mg	Max. Hardness = 25-27 scu @ 40 – 45 kN Disintegration Time = 15:15 – 15:45		
	Calcium Silicate	2.26%					
	Crospovidone	3.38 %					
	Microcrystalline Cellulose	31.58%					
124	Cab-O-Sil	0.75%	3.01%	1217.4 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.26%			15 kN	23 – 24 scu	4:00
	Crospovidone	5.08 %			30 kN	26 – 27 scu	15:00
	Microcrystalline Cellulose	31.58%					
128	Cab-O-Sil	0.84%	3.36%	1213 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.52%			15 - 18 kN	21 – 22 scu	9:30
	Crospovidone	3.79 %			20 kN	23 scu	13:00
	Microcrystalline Cellulose	34.29%			25 kN	23 – 24 scu	20:00
					30 kN	24 – 25 scu	---
					35 kN	23 – 25 scu	---
129	Cab-O-Sil	0.84%	3.36%	1233 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.52%			15 kN	23 – 24 scu	6:15
	Crospovidone	5.41 %			20 kN	23 – 25 scu	9:00
	Microcrystalline Cellulose	34.17%			25 kN	24 – 26 scu	13:30
					30 kN	24 – 26 scu	16:00
					35 kN	24 – 26 scu	20:00
133	Cab-O-Sil	0.84%	3.38%	1232.9 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.52%			15 kN	22 scu	15:30
	Crospovidone	5.41 %			20 kN	22 scu	18:30
	Microcrystalline Cellulose	26.46%			25 kN	23 scu	20:00
	Emdex	7.71%					
134	Cab-O-Sil	0.84%	3.53%	1232.9 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.52%			15 kN	24 – 25 scu	3:45
	Crospovidone	5.41 %			20 kN	25 – 26 scu	8:30
	Microcrystalline Cellulose	26.46%			25 kN	26 – 27 scu	11:00
	Prosolve® *	7.71%					
	*Microcrystalline Cellulose co-processed with 2% silica						
135	Syloid 244 FP	1.53%	3.79%	1240.8 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	2.26%			15 kN	22 – 26 scu	2:00 - 4:10
	Crospovidone	5.04%			20 kN	23 - 28 scu	4:00 - 8:40
	Microcrystalline Cellulose	30.06%			25 kN	25 - 29 scu	6:15 - 10:40
					30 kN	26 - 29 scu	8:20 - 11:30
136	Syloid 244 FP	1.50%	6.50%	1300.3 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	5.00%			15 kN	25 - 32 scu	1:30 - 3:45
	Crospovidone	5.00%			20 kN	27 - 34 scu	4:30 - 10:35
	Microcrystalline Cellulose	30.03%			25 kN	31 - 36 scu	7:15 - 13:00
					30 kN	31 - 36 scu	8:20 - 13:10
137	Cab-O-Sil	0.74%	5.77%	1142.3 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	5.03%			15 kN	18 - 19 scu	5:00 - 7:20
	Crospovidone	5.03%			20 kN	20 - 22 scu	11:45 – 13:30
	Microcrystalline Cellulose	20.05%			25 kN	21 - 23 scu	21:00 – 24:10
	Dicalcium Phosphate	10.02%			30 kN	21 - 22 scu	23:00 – 27:15
138	Syloid 244 FP	1.51%	4.74%	1156.8 mg	Comp Force	Hardness	Disintegration
	Calcium Silicate	3.03%			15 kN	21 - 22 scu	4:00 - 6:00
	Crospovidone	5.00%			20 kN	21 - 23 scu	9:00 – 11:20
	Microcrystalline Cellulose	10.00%			25 kN	21 - 22 scu	12:30 – 15:25
	Prosolve®	10.00%			30 kN	22 - 24 scu	13:45 – 19:45
	Dicalcium Phosphate	10.00%					

Exhibit 2

Summary of Development Batches

BATCH #	DESCRIPTION		Total added silica	Tablet Weight	Comp. Force vs. Hardness		
142	Syloid 244 FP Calcium Silicate Crospovidone Microcrystalline Cellulose	1.50% 5.00% 5.00% 25.47%	6.50%	1200 mg	Comp Force 15 kN 20 kN 25 kN 30 kN	Hardness 21 - 22 scu 21 - 23 scu 21 - 22 scu 22 - 24 scu	Disintegration 4:00 - 6:00 9:00 - 11:20 12:30 - 15:25 13:45 - 19:45
143	Syloid 244 FP Calcium Silicate Crospovidone Microcrystalline Cellulose	2.50% 4.00% 5.00% 25.47%	6.50%	1200 mg	Comp Force 15 kN 20 kN 25 kN 30 kN	Hardness not done 23 - 30 scu 25 - 30 scu 25 - 30 scu	Disintegration 4:00 - 19:00 17:00 - 20:00 10:30 - 21:00
205	Syloid 244 FP Calcium Silicate Crospovidone Microcrystalline Cellulose	3.50% 4.00% 5.00% 26.84%	7.5%	1300 mg	Comp Force 11.6 kN 13.7 kN 16.5 kN	Hardness 24 - 27 scu 26 – 31 scu 29 – 33 scu	Disintegration 1:33 - 2:05 2:45 - 3:40 3:10 - 5:10